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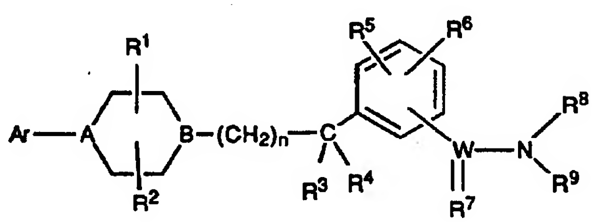

(I)

(57) Abstract

Compounds of general formula (I) are disclosed as novel antipsychotic agents.

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N-OXIDES OF 4-ARYLPIPERAZINES AND 4-ARYLPIPERIDINES AS ANTIPSYCHOTIC DRUGS

BACKGROUND OF THE INVENTION

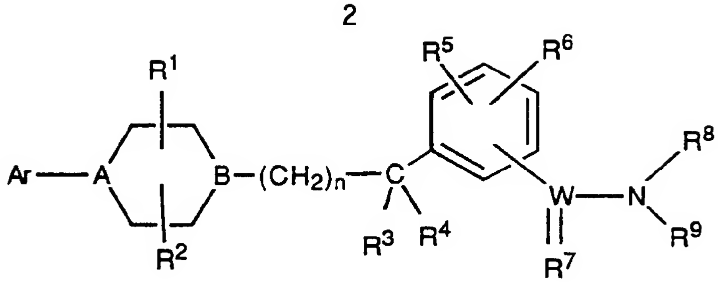
Antipsychotic drugs are known to alleviate the symptoms of mental illnesses such as schizophrenia. Examples of such drugs include phenothiazine derivatives such as promazine, chlorpromazine, fluphenazine, thioridazine and promethazine, thioxanthenes such as chlorprothixene, butyrophenones such as haloperidol and clozapine. While these agents may be effective in treating schizophrenia, virtually all except clozapine produce extrapyramidal side effects, such as facial tics or tardive dyskinesia. Since antipsychotics may be administered for years or decades to a patient, such pronounced side effects may complicate recovery and further isolate the individual from society.

Compounds having some structural similarity to those of the present invention are described in EPO application 88,309,581.2, U. S. Patent Nos. 4,772,604; 4,782,061; 4,362,738; 3,988,371; 4,666,924; 4,931,443; and 4,992,441. Other somewhat similar compounds are disclosed in *J. Clin. Chem. Clin. Biochem.* **1988**, *26*, 105 and *J. Med. Chem.*, **1991**, *34*, 2133.

The present invention describes novel compounds that display activity in mammals suggestive of antipsychotic activity in man. The receptor binding profile shows only weak affinity for the dopamine-2 receptor, which may be an indication that the N-oxide functionality is being metabolically reduced *in vivo* to the corresponding piperazines and piperidines. Such piperazines and piperdines are disclosed and claimed in WO 9304682, 18 Mar 1993. See also application Serial No. 944,006, filed September 11, 1992.

SUMMARY OF THE INVENTION

Compounds of the general formula I:

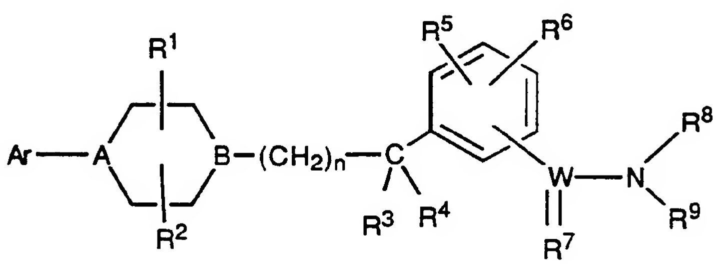


I

wherein Ar, W, A, B, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9 and n, as defined hereinafter, are potent antipsychotic agents useful in the treatment of psychotic conditions such as schizophrenia in animals and humans. The compounds of the present invention may also be useful in the treatment of other disorders of the central nervous system such as anxiety and aggression.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to compounds represented by the general formula **I**:



I

wherein

A is N, CH, or N^+-O^-.

B is N, or N^+-O^-; with the proviso that when A is N or CH, B must be N^+-O^-; and when A is N^+-O^-, B must be N.

W is C or SO. More preferably, W is C.

R^1 and R^2 are independently selected from any of H or C_1-C_4 alkyl. More preferably, R^1 and R^2 are each H.

n = 0-4 and more preferably n=0.

R^3 and R^4 are either both H, or one of them is H and the other is C_1-C_4 alkyl or hydroxyl, or both are taken together as oxygen to form a carbonyl group with the attached carbon atom; except when n = 0. More preferably, R^3 and R^4 are each H.

R^5 and R^6 are independently selected from any one of H, C_1-C_8 alkyl, C_1-C_8 alkoxy, nitro, halogen, haloalkyl, C_1-C_8 alkylthio, amino, C_1-C_8 mono- or dialkyl amino, or C_1-C_8 alkylamido. Preferably, R^5 and R^6 are independently selected from any one of H, C_1-C_8 alkyl, C_1-C_8 alkoxy, nitro, amino, or C_1-C_8 alkylamido and most preferably R^5 and R^6 are each H.

R^7 is O or S where W is C; and R^7 is O where W is SO. More preferably, R^7 is O.

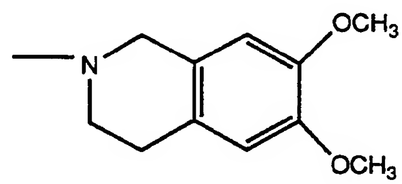
R^8 and R^9 are independently selected from any one of H, C_1-C_8 alkyl, phenyl, substituted phenyl, aralkyl wherein the alkyl portion is C_1-C_8, alkoxycarbonylamido, acyl, C_3 to C_{10} cycloalkyl; or -NR^8R^9 may be taken together to form a ring having 4-10 ring atoms, preferably 4-8 ring atoms, which ring may be saturated or unsaturated, preferably saturated, substituted or unsubstituted, and may contain up to one more hetero atoms in addition to the ring N, such as S, O or N within the ring; more preferably, the additional hetero atoms are N or O; even more preferably, the additional hetero atom is O; and most preferably, there are no additional hetero atoms; or optionally the -NR^8R^9 ring may be combined with a 2-4 membered carbon moiety to form a fused bicyclic ring, which may be saturated or unsaturated, and unsubstituted or substituted; or optionally the NR^8R^9 ring may be combined with a four membered moiety containing at least two carbon atoms and up to two hetero atoms selected from S or O, but preferably selected from O, to form a spirocycle ring system which may be saturated or unsaturated, preferably saturated, substituted or unsubstituted. More preferably, the 2-4 membered carbon moiety is combined with a -NR^8R^9 ring which contains 5-7 ring atoms with the N being the only hetero atom in the ring,thereby forming a fused ring system. Most preferably, the -NR^8R^9 ring is saturated prior to being fused with the 2-4 membered carbon moiety. Most preferably, R^8 and R^9 are taken together with the N to form a 6 membered fully saturated ring which may be substituted or unsubstituted.

When -NR^8R^9 are taken together to form a ring, a fused ring system or a spirocycle ring system, such rings may be independently substituted with any of C_1-C_8 alkyl, C_1-C_8 alkoxy, phenyl, substituted phenyl (wherein phenyl may be substituted with any of the substituents listed hereinafter for R^{10} or R^{11} substituted phenyl), hydroxy, aralkyl such as benzyl, wherein the alkyl portion is C_1-C_8, oxo or thioxo. The preferred substituents for the

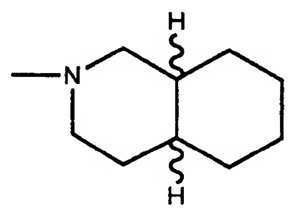
$-NR^8R^9$ ring are C_1-C_8 alkyl, hydroxy or oxo.The preferred substituents for the fused ring system are C_1-C_4 alkoxy. The spirocycle ring system is preferably unsubstituted and saturated.

Examples of preferred ring systems wherein $-NR^8R^9$ are taken together to form a ring having 4-10 ring atoms include pyrrolidine, piperidine, hexahydroazepine, octahydroazocine, oxazine and 2,6-dimethylpiperidine.

Examples of preferred fused ring systems for $-NR^8R^9$ are represented by formulas **III** and **IV**:

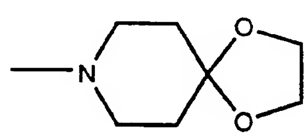


III



IV

As used herein for the definition of $-NR^8R^9$, a spiro ring system is a 2 ring system, the union of which is formed by a single atom which is the only common member of the two rings. A particularly preferred spirocycle ring is represented by the formula **V**:

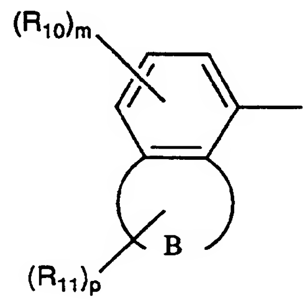


V

Ar is aryl such as phenyl or naphthyl, heteroaryl or substituted aryl wherein aryl may be independently substituted with one or more of C_1-C_8 alkyl, cycloalkyl, hydroxyalkyl, C_1-C_8 alkoxy, aryloxy, hydroxyl, trifluoromethyl, trifluoromethoxy, cyano, C_1-C_8 alkylthio, halogen, nitro, C_1-C_8 haloalkyl, amino or C_1-C_8 mono- or di-alkylamino. Alkoxy, such as i-propoxy or methoxy are presently the preferred substituents. As a halogen, the substitution is preferably fluorine, chlorine, or bromine. Optionally,

present hydroxyl or hydroxyalkyl groups may be esterified or etherified. Examples of suitable heteroaryl rings are pyrimidinyl, pyridinyl, pyridazinyl, pyrazinyl, imidazyl, pyrrole, furan, thiophene, triazolyl, and thiazolyl. The preferred heteroaryl rings are pyrimidinyl and pyridinyl. More preferably, Ar is substituted phenyl.

Ar may also be a fused ring system of the formula **II**:



II

wherein B together with the 2 carbon atoms of the phenyl group forms an entirely or partly unsaturated cyclic group having 5-7 ring atoms and within the ring 0-3 hetero atoms from the group O, S and N may be present with the proviso that the sum of the number of oxygen atoms and sulfur atoms is at most 2, and that the nitrogen atoms in the ring may be substituted with R^{12} selected from any one of H, C_1-C_8 alkyl, hydroxyalkyl or C_1-C_8 acyl;

R^{10} and R^{11} may be independently selected from any one of alkyl, cycloalkyl, phenyl, substituted phenyl or heteroaryl, hydroxyalkyl, alkoxyalkyl, alkoxy, aryloxy, alkylthio, arylthio, mono- or dialkylamino, mono- or diarylamino, hydroxyl, amino, alkyl-, alkoxy-, amino-, or mono- or dialkylamino-carbonyl, nitro, cyano, halogen, trifluoromethyl, trifluoromethoxy, amino or mono- or dialkylaminosulfonyl. R^{10} may also be an oxo or thioxo group. Variable m has the value 0-3 and p has the value 0-2. More preferably, R^{10} and R^{11} are selected from any of alkoxy, halogen or cyano.

More preferred values for the moiety of formula II are: B forms together with the two carbon atoms of the phenyl group an entirely or partly unsaturated ring consisting of 5 atoms, which ring comprises at least one oxygen atom. R^{10} and R^{11} are selected from any of alkyl, alkoxy, hydroxyl, nitro, cyano, halogen, or trifluoromethyl. R^{10} and R^{11} are more preferably selected from any of alkoxy, halogen or cyano. R^{10} is preferably in the meta

or ortho position in relation to the piperazine/piperidine group. Variables m and p have the value 0-2. A particular preferred subgensis of such compounds are those wherein m and p each have a value of 0.

When R^{10} or R^{11} comprises an alkyl group, it is preferably a straight or branched alkyl group having 1-5 carbon atoms. As a cycloalkyl group, the groups R^{10} or R^{11} comprise a ring system having 3-7 ring atoms and not more than 10 carbon atoms including any substituents as a whole. When R^{10} or R^{11} is a hydroxyalkyl group such a group preferably comprises 1-5 carbon atoms. As a halogen atom, R^{10} or R^{11} preferably is fluorine, chlorine or bromine. Optionally present hydroxyl or hydroxyalkyl groups may be esterified or etherified.

When R^{10} or R^{11} is substituted phenyl it may be substituted with one or more of C_1-C_8 alkyl, C_1-C_8 alkoxy, halogen, trifluoromethyl, C_1-C_8 alkylthio, dialkylamino (wherein each alkyl is C_1-C_8), C_1-C_8 alkylamino, nitro or mono- or dialkylamino sulfonyl (wherein each alkyl is C_1-C_8).

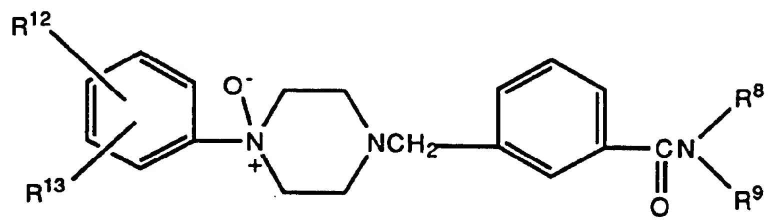
As used herein, unless otherwise noted alkyl and alkoxy whether used alone or part of a substituent group, include straight and branched chains. For example, alkyl radicals include methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, 2-methyl-3-butyl, 1-methylbutyl, 2-methylbutyl, neopentyl, n-hexyl, 1-methylpentyl, 2-methylpentyl. Alkoxy radicals are oxygen ethers formed from the previously described straight or branched chain alkyl groups. Of course, if the alkyl or alkoxy substituent is branched there must be at least 3 carbon atoms.

The term “aryl” as used herein alone or in combination with other terms indicates aromatic hydrocarbon groups such as phenyl or naphthyl. The term "heteroaryl" means aromatic hydrocarbon groups containing 1 or 2 hetero atoms selected from any of S, O or N. The term “aralkyl” means a C_1-C_8 alkyl group substituted with an aryl group. The term acyl, unless otherwise specified herein, means a benzoyl or a C_1-C_8 alkanoyl group , which can be optionally substituted. With reference to substituents, the term independently means that when more than one of such substituent is possible such substituents may be the same or different from each other.

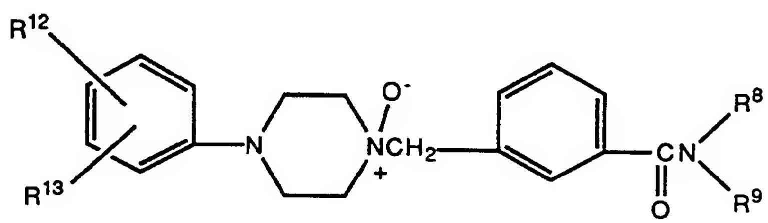
Compounds according to this invention have a 1,2-, 1,3- or 1,4-relationship of the W substituent with the -C(R^3)(R^4)- group on the W-bearing

phenyl ring. Preferred compounds have a 1,2- or 1,3- relationship of these two groups. The R^5 and R^6 substituents may be located in any of the other unsubstituted ring positions.

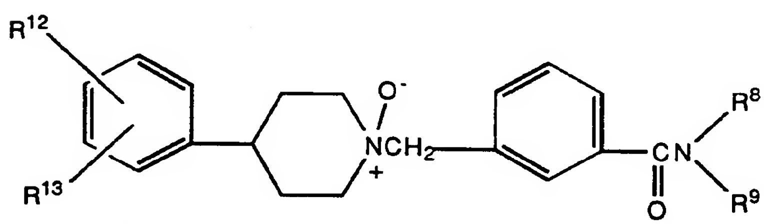
Particularly preferred subgenuses of compounds of the formula **I** are those of the formula **(Ia-Ic)**:



Ia



Ib



Ic

wherein R^8 and R^9 are as defined above and R^{12} and R^{13} are as defined as substituents for Ar in formula I. Preferably, R^8 and R^9 are taken together with the N to form a saturated ring having 5-8 ring atoms and one of R^{12} and R^{13} is C_1-C_8 alkoxy and the other is H. The most preferred C_1-C_8 alkoxy groups are i-propoxy or methoxy.

Examples of particularly preferred compounds include:

1-[3-[[4-[2-(1-Methylethoxy)phenyl]-4-oxide-1-piperazinyl]methyl]-benzoyl]piperidine;

1-[3-[[4-[2-(1-Methylethoxy)phenyl]-1-piperazinyl-1-oxide]methyl]-benzoyl]piperidine; and

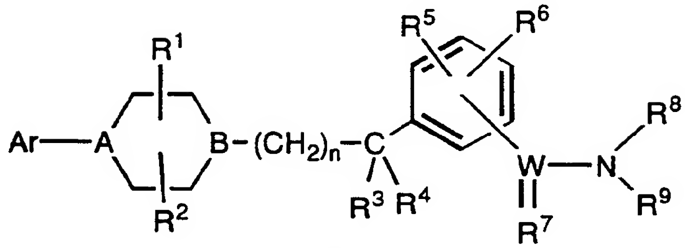
1-[3-[[4-[2-(1-Methylethoxy)phenyl]-1-piperidinyl-1-oxide]methyl]-benzoyl]piperidine monohydrochloride.

The invention definition of formula I includes racemates and individual isomers, e.g. as caused by the presence of a stereogenic carbon such as when a substituent would be 2-butyl. Also within the scope of the invention are compounds of the invention in the form of hydrates and other solvate forms.

Representative salts of the compounds of formula I which may be used include those made with acids such as hydrochloric, hydrobromic, hydroiodic, perchloric, sulfuric, nitric, phosphoric, acetic, propionic, glycolic, lactic, pyruvic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, benzoic, cinnamic, mandelic, methanesulfonic, ethanesulfonic, hydroxyethanesulfonic, benzenesulfonic, p-toluenesulfonic, cyclohexanesulfamic, salicyclic, p-aminosalicyclic, 2-phenoxybenzoic, 2-acetoxybenzoic or a salt made with saccharin. Such salts can be made by reacting the free base of formula I with the acid and recovering the salt.

The compounds of formula I may be prepared according to Reaction Scheme 1.

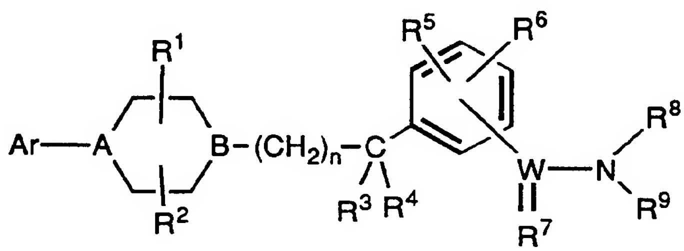
Reaction Scheme 1



II

Where A and B do not equal $N^+\text{-}O^-$

↓ Oxidant



I

Where A and B are as defined in herein

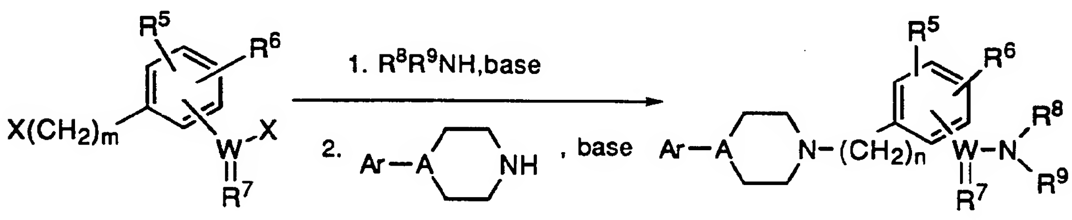
As shown, oxidant refers to any reagent or reagent mixture capable of transfering an oxygen to a nitrogen atom to convert it to the N-oxide functionality. Examples of such reagents are peracids, such as m-choroperoxybenzoic acid and peracetic acid. Suitable solvents would include halogenated solvents such as methylene chloride and chloroform. Another reagent capable of effecting this transformation is ruthenium on carbon (5 %) in the presence of sodium acetate, acetic acid, and peracetic acid. Occasionally, the products can be obtained immediately from the reaction without the need for chromatographic purification. However, when there are two possible sites of oxidation (e.g. with a piperazine, A = B = N), the two different singly oxidized compounds (A = $N^+\text{-}O^-$, B = N and B = N, A = $N^+\text{-}O^-$) can be separated from each other by chromatographic methods such as by flash column chromatography on silica gel.

The requisite piperazines and piperidines of formula **II** described herein and in Examples 1-3 are prepared as described in WO 9304682 (18 Mar 1993), being a CIP of WO 9304684 (18 Mar 1993). More specifically,

the requisite piperazines and piperidines of formula **II** may be prepared as described in Reaction Schemes 2-8.

The compounds of formula **II** may be prepared according to Reaction Scheme 2:

Reaction Scheme 2

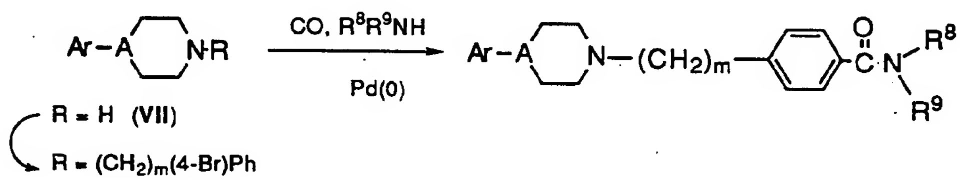


As shown, the 1,2-, 1,3-, and 1,4-disubstituted benzamides or sulfonamides may be prepared by a sequential reaction with the appropriate haloalkyl benzoyl halide or haloalkyl benzenesulfonyl halide (**VI**). The first condensation with the requisite amine is conducted in a non-protic solvent such as tetrahydrofuran (THF) with cooling (e.g. in the range -78°C to 5°C), being careful not to let the solution exotherm so as to avoid reaction of the haloalkyl functionality. The base present in the reaction (for the removal of the HX formed) is typically a tertiary amine such as triethylamine or di-isopropylethylamine, or it could be a molar excess (at least) of the amine reactant (e.g. R^8R^9NH). The intermediate haloalkyl benzamide thus formed could be then taken on directly to the product by reaction with the aryl piperazine or aryl piperidine (**VII**), or it could be isolated after an extractive workup and/or chromatography. If the intermediate was carried on in situ to the product (**VIII**) in THF, heating (30°C-67°C) is generally required for complete reaction. If the intermediate is isolated and then reacted separately with the aryl piperazine or aryl piperidine, the optimal solvents are dipolar aprotic solvents such as dimethylformamide (DMF) or N-methyl-2-pyrrolidinone. The base used in this latter step could be a tertiary amine or potassium or sodium carbonate. Using the two-step method (i.e. isolation of the intermediate), the product could in some cases be obtained pure after recrystallization as a salt without resort to chromatography.

1,2- and 1,3-Halomethylbenzoyl halides used when m=1 in Reaction Scheme 2 are commercially available from Fluka, Carbolabs or Pfaltz and Bauer, or could be prepared by literature methods or modifications thereof. (See e.g.: Ger. Offen. 2,835,440, 28 Feb. 1980; and J. Johnson and I. Pattison *J. Hetero. Chem.* **1986**, *23*, 249). Halomethyl benzoyl halides bearing substituents have also been described in the literature, such as in the methoxy-substituted case cited in R. Quelet et al. *Bull. Soc. Chem., France* **1969**, 1698. The final products are typically chromatographed to achieve purity, and then converted to an acceptable salt form.

The 1,3- or 1,4-disubstituted analogs may be prepared in the same manner as the derivatives shown above. There are alternative methods for the preparation of compounds of this type. For example, they may be synthesized by a palladium-mediated coupling of a bromoaryl derivative with carbon monoxide and piperidine (*J. Org. Chem.* **1974**, *39*, 3327) as shown in Reaction Scheme 3 for a 1,4-disubstituted case.

Reaction Scheme 3

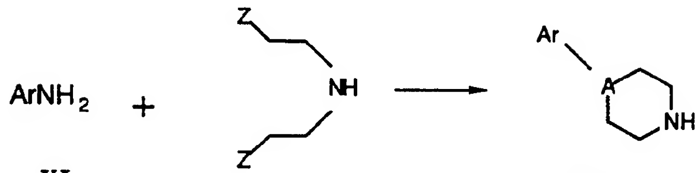


IX X

The preparation of the sulfonamide analogues (W = SO, R^7 = O, and n = 0 in **II**) require preparation of the necessary halomethyl sulfonyl halide by halogenation of the appropriate toluenesulfonyl halides on the benzylic methyl position with N-bromosuccinimide mediated by benzoyl peroxide. The halomethyl sulfonyl halides were used in generally the same manner as for the benzoyl halide case (e.g. see Reaction Scheme 3).

Many aryl piperazines are commercially available from Aldrich Chemical Company or may be prepared by standard methods known in the art (for example see G. E. Martin et al. *J. Med. Chem.* **1989**, *32*, 1052). These piperazines (**VII**, A=N) may be obtained according to the following Reaction Scheme 4 where Ar is as described in connection with formula **II** and Z is a leaving group such as halo (e.g. chloro):

Reaction Scheme 4



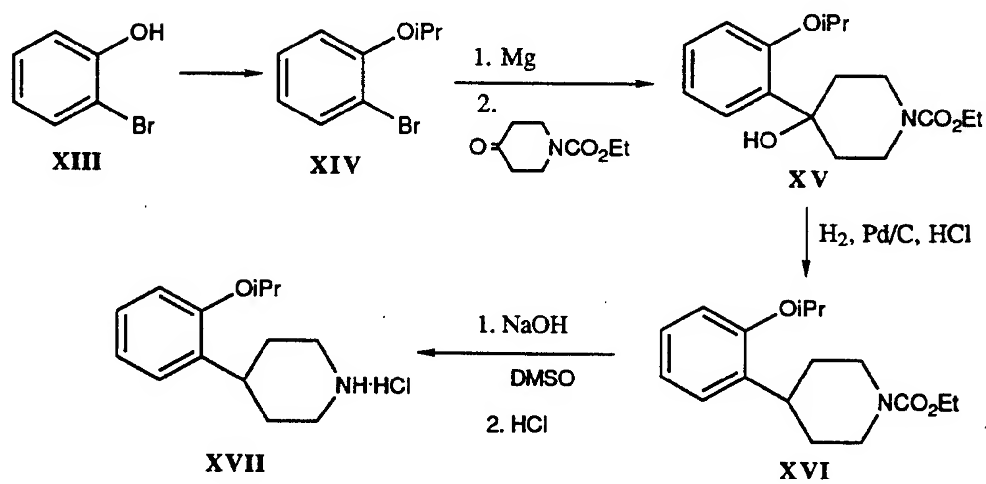
XI XII VII (X = N)

In carrying out Reaction Scheme 4, compound **XII** is heated with an aniline or an aromatic heterocyclic primary amine **XI** at about 50 to 120°C in a solvent such as n-butanol with recovery of the piperazine **VII** (A=N).

Piperazines of formula **VII** (A=N) where Ar is a formula **II** moiety are described as formula (2) in U.S. Patent 4,782,061 published earlier as EPO 185,429 and EPO 190,472 on June 15, 1986 and August 13, 1986, respectively, which documents are hereby incorporated by reference. Other piperazines of formula **VII** (A=N) where Ar is a formula **II** moiety are described as formula 29 in EPO 138,280 published April 24, 1985 which is incorporated by reference. In addition, some of the piperazines of formula **VII** can be prepared by the method of ten Hoeve et al. (*J. Org. Chem.* **1993**, *58*, 5101), involving the displacement of a methoxy aromatic by piperazine or a piperazine derivative.

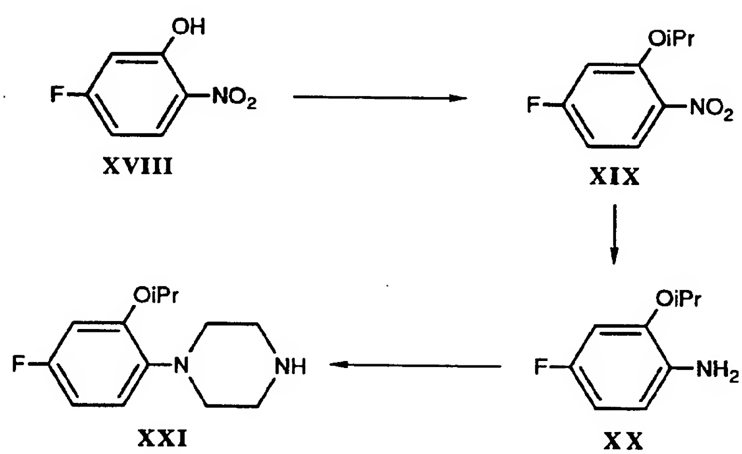
Other piperazines may be prepared by the method of I. van Wijngaarden et al. (*J. Med. Chem.* **1988**, *31*, 1934). Other piperidines may be prepared by the method shown in Reaction Scheme 5.

Reaction Scheme 5



Other piperazine may be synthesized as shown in Reaction Scheme 6.

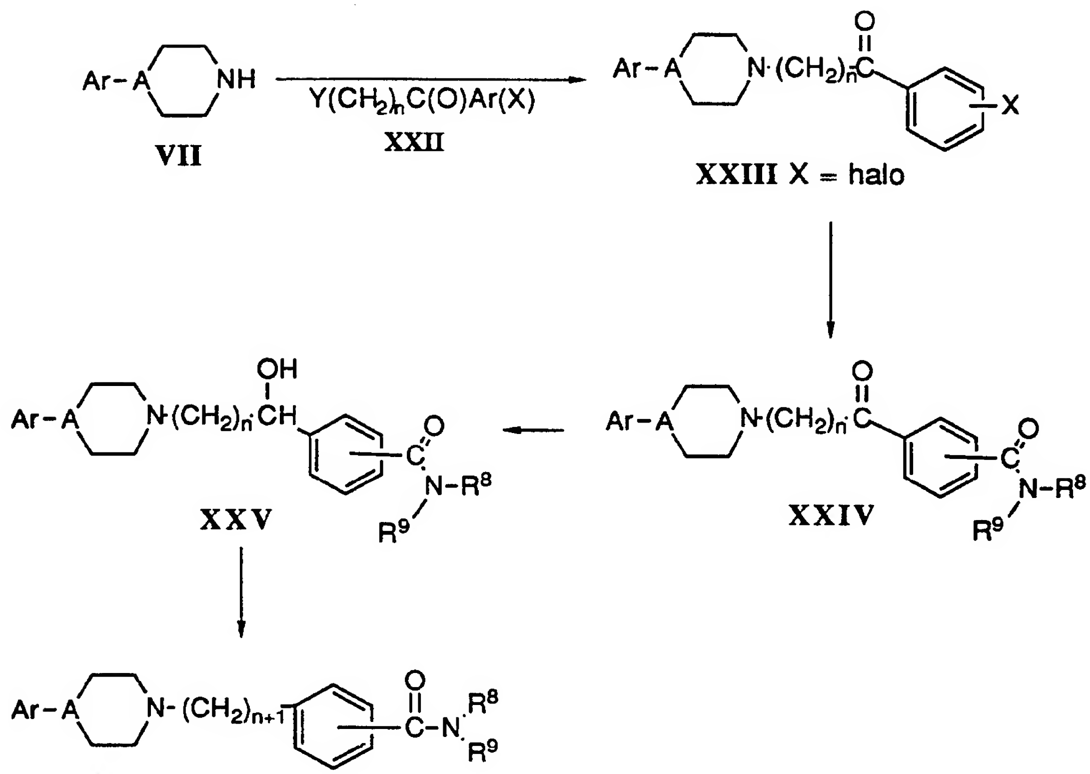
Reaction Scheme 6



The piperazines required to prepare 2-fluoropiperazinyl compounds may be prepared by nucleophilic displacement of 1,2-difluorobenzene with the requisite piperazine such as in reaction of 2,5-dimethylpiperazine with 1,2-difluorobenzene in the presence of sodium amide.

Alternatively, certain other compounds useful in making the compounds of the invention can be prepared by the method shown in Reaction Scheme 7.

Reaction Scheme 7

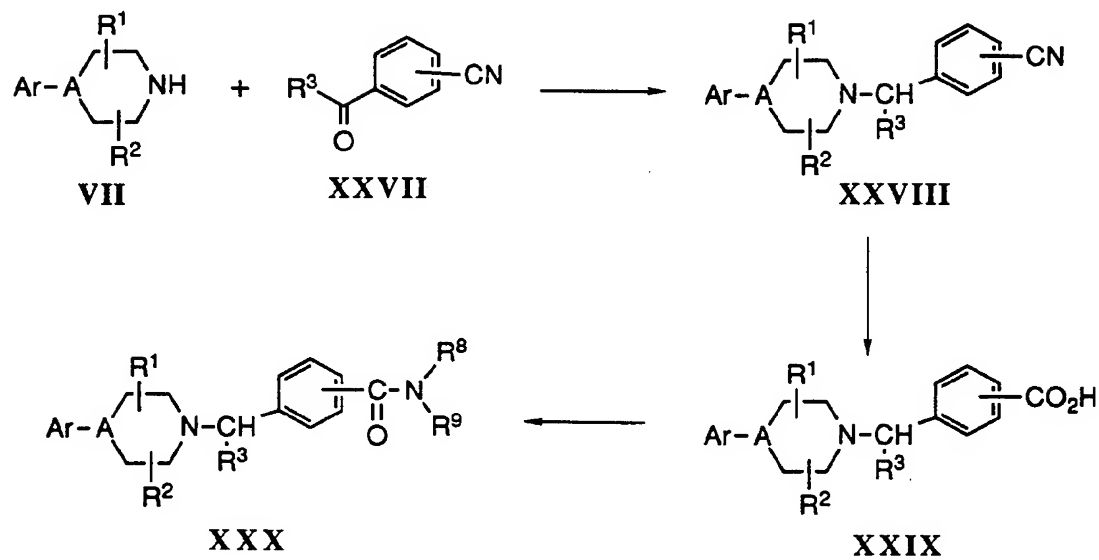


XXVI

Aryl piperazines **VII** (A=N) can be condensed with compounds **XXII** in which Y represents a leaving group suitable for a diplacement reaction (e.g. halogen, p-toluenesulfonate, trifluoromethanesulfonate) to give compounds **XXIII.** This deplacement reaction is typically carried out in a dipolar aprotic solvent such as DMSO or DMF, using sodium carbonate, potassium carbonate, or a tertiary amine [e.g. triethylamine or di(isopropyl)ethylamine] as the base, generally with heating (30-80°C for 2h to 4d). The resulting ketone (**XXIII**) can be converted to amide **XXIV** by the aminocarbonylation reaction described for Reaction Scheme 3. Reduction of the carbonyl group of **XXIV** by the use of sodium borohydride in alcoholic solvents (EtOH, iPrOH) at room temperature (2-30h) can gave alcohol **XXV**. Further reduction of **XXV** by the method of catalytic hydrogenation (H_2, palladium/carbon) in alcoholic solvents (e.g. EtOH), in the presence of added mineral acid (e.g. HCl) to facilitate the reaction, can afford compounds **XXVI**.

Compounds of formula II may also be prepared by the chemistry shown in Reaction Scheme 8.

REACTION SCHEME 8



Carbonyl compound **XXVII** is reacted with compounds **VII** in a reductive amination reaction to give compounds **XXVIII**. This reaction can be carried out using sodium borohydride in titanium isopropoxide. It can also be conducted by forming an imine from **VII** and **XXVII** and then reducing it catalytically with hydrogen in the presence of a noble metal catalyst (e.g. palladium or platinum). Hydrolysis of the nitrile functionality of **XXVIII** to give **XXIX** is carried out in the presence of sodium hydroxide or potassium hydroxide, usually at reflux in an alcoholic solvent. Compound **XXIX** is then combined with R^8R^9NH to form amide **XXX**, using one of the standard reactions to accomplish this transformation such as the use of dicyclohexylcarbodiimide or carbonyl diimidazole.

The antipsychotic activity of the compounds of the invention may be determined by the Block of Conditioned Avoidance Responding (Rat) test (CAR), references being Cook, L. and E. Weidley in *Ann. N.Y. Acad. Sci.*, **1957,** 6, 740-752, and Davidson, A.B. and E. Weidley in *Life Sci.*, **1976,** 18, 1279-1284. This test was performed for compounds disclosed in this invention, and the data are listed in Table 1. A reading of -20% in the CAR test was generally taken to represent a minimum value for a compound to be designated as active at a given dose. In addition, the affinity of the

compounds for several receptors found in the central nervous system was evaluated; the affinity for the D-2 (dopamine-2) receptors is also listed in Table 1. As modulation of this receptor is generally recognized to be beneficial in the treatment of schizophrenia (G. P. Reynolds *Trends Pharmacol. Sci.* **1992**, *13*, 116), affinity for this receptor indicates potential utility for the compounds. A D-2 affinity of 1000 nM or less has been taken as predictive of antipsychotic activity.

Block of Conditioned Avoidance Responding (Rat)

Apparatus: Rat operant chambers, housed within sound attenuated booths, both from Capden Instruments Ltd., were used in this test. The test chamber (8" H x 90-3/8" W x 9" D) is constructed of aluminum and plexiglass with floor grid bars of stainless-steel (1/8" O.D.) spaced 9/16" apart. A stainless-steel operation level 1-1/2" wide projects 3/4" into the chamber and is positioned 2-2/8" above the grid floor. The shock stimulus is delivered via the grid floor by a Coulbourn Instruments solid state module. The parameters of the test and the collection of data are controlled automatically.

Training: Male, Fischer 344 rats obtained from Charles River (Kingston, NY) weighing more than 200 g, are individually housed with chow and water provided ad libitum. The rats are trained for two weeks to approach criterion levels in the avoidance test (90% avoidance rate). One-hour training sessions are run at about the same time each day for four or five days a week. The training session consists of 120 trials, with the conditioned stimuli presented every 30 sec. A trial begins with presentation of the conditioned stimuli (a light and a tone). If the rat responds by depressing the operant lever during the 15-second presentation of the conditioned stimuli, the trial is terminated and the animal is credited with a CAR. Failure to respond during the conditioned stimuli causes the presentation of the unconditioned stimulus (UCS), a 0.7 mA shock which is accompanied by a light and tone for five seconds. If the rat depressed the lever within the ten-second period, the shock and trial are terminated and an escape response recorded. If the rat fails to depress the lever during the UCS (shock), the trial is terminated after ten seconds of shock and the absence of a response is scored as a failure to escape. Intertrial level presses have no effect. If a rat performs at the 90% CAR level for two weeks, it is then run twice a week on the test schedule (see below) until baseline performance stabilized. Before any

drug is administered, two weeks of CAR at a rate of 90% or better is required.

The percent change in CAR on the drug treatment day compared to vehicle pretreatment day is the key measure. The percent change (% change) in CAR is determined using the following formula:

% change CAR = ((% CAR for Day 2/% CAR for Day 1) x 100)-100

A negative number indicates a blockade of CAR, whereas a positive number would indicate increased CAR. The test results are reported as the mean % change for the group of rats. Failure to escape, a measure of the general sedative potential of the compound, was calculated for each animal as follows:

% Failures = # of Failures to Escape/# of trials

The % failures, viz., loss of escape, is also reported as a group mean. Failures to escape are monitored closely and a session is terminated if ten failures occurred. ED_{50} values and 95% confidence limits are calculated using linear regression analysis. The results of the CAR tests are shown in Table I.

In the Table and formulas therein, OiPr is isopropoxy, Me is methyl, and NT is not tested in that particular test. The escape loss numbers are shown at CAR 15 mg/kg ip.

Receptor Binding Assay

The dopamine D_2 binding activity of compounds was determined using a P_2 fraction (synaptosomal membranes) prepared from male, Wistar rats. The D_2 assay employed a P_2 fraction from the striatum, the ligand ^{3}H-spiperone at a concentration of 0.05 nM, and 1 mM haloperidol as a blank determinant. Incubation was in 3 mM potassium phosphate buffer for 45 min at 37°C. Under these conditions, specific binding constituted 75% of total binding, and the K_I values for some known drugs were: 0.37 nM for haloperidol and 82 nM for clozapine.

The data from this assay were analyzed by calculating the percent inhibition of the binding of the tritiated ligands by given concentrations of the test compound. K_I values, where given, were obtained from the logit analysis of concentration-inhibition curves.

To prepare the pharmaceutical compositions of this invention, one or more compounds or salts thereof of the invention, as the active ingredient, is intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed. Thus for liquid oral preparations, such as for example, suspensions, elixirs and solutions, suitable carriers and additives include water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like; for solid oral preparations such as, for example, powders, capsules and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar coated or enteric coated by standard techniques. For parenterals, the carrier will usually comprise sterile water, though other ingredients, for example, for purposes such as aiding solubility or for preservation, may be included. Injectable suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents and the like may be employed. The pharmaceutical compositions herein will preferably contain per dosage unit, e.g., tablet, capsule, powder, injection, teaspoonful and the like, from about 50 to about 100 mg of the active ingredient, although other unit dosages may be employed.

In therapeutic use as an antipsychotic agent in mammals, the compounds of this invention may be administered in an amount of from about 0.5 to 5 mg/kg per day, and more preferably 1-3 mg/kg per day. The dosages, however may be varied depending upon the requirements of the patient, the severity of the condition being treated and the compound being employed. Determination of optimum dosages for a particular situation is within the skill of the art.

The following Examples illustrate the present invention, but are not deemed to be limiting. Examples 1-3 describe the preparation of specific compounds listed in the Table which follow the Examples.

EXAMPLE 1

1-[3-[[4-[2-(1-Methylethoxy)phenyl]-4-oxide-1-piperazinyl]methyl]benzoyl]piperidine 1.7Hydrate (Compound 1)

1-[3-[[4-[2-(1-Methylethoxy)phenyl]-1-piperazinyl]methyl]benzoyl]-piperidine (15 g, 35.6 mmol) was treated with m-chloroperoxybenzoic acid (6.15 g, 35.6 mmol) dissolved in chloroform (100 mL). This solution was allowed to stir overnight, and the solvent was then removed. The residue was purified on a silica gel column ($CHCl_3$/MeOH; 100:0 to 90:10). The first component isolated consisted of unreacted starting material (9.8 g). The second component isolated (380 mg) was recrystallized from methylene chloride/ether, and was identified to be the title compound by analysis of the H-1 NMR spectrum (400-MHz, CD_3OD) and mass spectrum as a white powder, mp 98-101°C. The compound was labile to prolonged heating in methanol, and was kept in the refridgerator. ^1H NMR (CD_3OD, 250 MHz) δ 8.4 (d, 1H), 7.4 (m, 4H), 7.3 and 7.2 (both d, 1H each), 7.1 (t, 1H), 4.9 (m, 3H), 3.7 (d, 4H), 3.4 (s, 2H), 3.15 (t, 2H), 2.8 and 2.9 (both d, 2H each), 1.7 (m, 4H), 1.5 (d, 6H).

Elemental Analysis: Calculated for $C_{26}H_{35}N_3O_3 \cdot 1.7H_2O$: C, 66.71; H, 8.21; N, 8.98; H_2O, 6.54. Found: C, 66.90; H, 7.97; N, 8.62; H_2O, 6.15.

EXAMPLE 2

1-[3-[[4-[2-(1-Methylethoxy)phenyl]-1-piperazinyl-1-oxide]methyl]benzoyl]piperidine 1.1Perchlorate 0.4Hydrate (Compound 2)

The third component to be isolated from the chromatography described in Example 1 was the title compound listed, 2.62 g, indicating a 3.4:1 preference for oxidation of the benzylic amine relative to the aniline nitrogen. This material was dissolved in MeOH (ca. 10 mL) and treated with 70% aqueous perchloric acid, and then triturated with ether, causing the perchlorate salt of the title compound to emerge. Analysis of the H-1 NMR spectrum (400-MHz, CD_3OD) and mass spectrum of the compound confirmed the structure indicated. ^1H NMR (CD_3OD, 250 MHz) δ 7.65 (d, 1H), 7.6 (m, 3H), 7.0 (m, 3H), 6.9 (t, 1H), 4.95 (s, 2H), 4.65 (q, 1H), 4.0 (t, 2H), 3.7 (m, 4H), 3.6 (d, 2H), 3.35 (m, 4H), 1.7 (m, 4H), 1.55 (m, 1H), 1.35 (d, 6H).

Elemental Analysis: Calculated for $C_{26}H_{35}N_3O_3 \cdot 1.1HClO_4 \cdot 0.4H_2O$: C, 56.23; H, 6.65; N, 7.56; Cl, 7.02; H_2O, 1.29. Found: C, 56.01; H, 6.64; N, 7.08; Cl, 7.36; H_2O, 1.21.

EXAMPLE 3

1-[3-[[4-[2-(1-Methylethoxy)phenyl]-1-piperidinyl-1-oxide]methyl]benzoyl]-cis-2,6-dimethylpiperidine 0.6Hydrate 0.25Chloroform (Compound 3)

A mixture of 2-bromophenol (23.2 mL, 0.20 mol), potassium carbonate (33.2 g, 0.24 mol) and 2-bromopropane (28.0 mL, 0.30 mol) in dimethylformamide (200 mL) was stirred in a preheated oil bath (60°C) for 5 h. The cooled reaction mixture was then partitioned between ether and water. The layers were separated and the aqueous phase was extracted with ether. The combined organic solution was washed with copious amounts of water, 3N aqueous NaOH, dried ($MgSO_4$), filtered and concentrated in vacuo to furnish 39.3 g (91%) of 2-(isopropoxy)bromobenzene as a pale yellow oil which was carried on without further purification. The structure was supported by GC/MS and 90 MHz ^1H NMR.

To a suspended solution of Mg chips (10.07 g, 0.414 mol) in anhydrous ether (150 mL) at 22°C under argon was added ca. 0.15 mL of 1,2-dibromoethane. Then 43.7 g (0.200 mol) of 2-(isopropoxy)bromobenzene in 200 mL of ether was added dropwise. After 50% of the aryl halide was added, the reaction began to reflux vigorously. The flask was cooled in an ice bath. After the refluxing had subsided somewhat, the ice bath was removed and the remaining aryl halide was added over a 1.5 h period. The resultant Grignard reagent was cooled in a dry ice/ether bath for 2 h and then treated with 34.0 mL (0.221 mol) of 98% 1-carbethoxy-4-piperidone. Upon complete addition of ketone, the reaction mixture was allowed to warm to 22°C and stirred for 2 h. The reaction was then quenched with cold aqueous ammonium chloride which resulted in an emulsion. Addition of 1M aqueous HCl solution separated the two layers. The aqueous phase was extracted with additional ether and the combined organic solution was washed with 10% aqueous sodium bisulfite, 1.0 M HCl, saturated $NaHCO_3$, and dried (K_2CO_3). Filtration and concentration yielded 56.36 g of 1-carbethoxy-4-[2-(1-methylethoxy)phenyl]-4-piperidinol as a yellow viscous oil which was carried on without further purification The structure of this oil was supported by ^1H NMR.

A crude solution of 1-carbethoxy-4-[2-(1-methylethoxy)phenyl]-4-piperidinol (36 g), 10% palladium on carbon (1.80 g), 5 mL of concentrated HCl and 125 mL of MeOH was shaken on a Parr apparatus under 55.5 psig of hydrogen at 22°C for 3 d. The reaction was filtered over Celite, and concentrated to a residue. This material was partitioned between ether and water. The organic solution was dried ($MgSO_4$), filtered, and concentrated to yield 29.34 g of 1-carbethoxy-4-[2-(1-methylethoxy)phenyl]piperidine as a light yellow oil which was carried forward without further purification. The structure was supported by MS and ^1H NMR.

A mixture of crude 1-carbethoxy-4-[2-(1-methylethoxy)phenyl]piperidine (29.3 g) and sodium hydroxide pellets (6.12 g, 0.106 mol) in DMSO (100 mL) was stirred in a preheated oil bath at 100°C for 4 d. The reaction mixture was then poured into water (200 mL) and the crude product was extracted into methylene chloride. The methylene chloride extracts were dried over $MgSO_4$, filtered and concentrated to afford 21.34 g of a crude dark brown oil. This oil was dissolved in 1N aqueous HCl solution and washed with ether. The acidic aqueous solution was basified with 3N NaOH and the product was extracted into methylene chloride. The combined methylene chloride extracts were dried ($MgSO_4$), filtered and concentrated to yield 13.34 g of a semi-solid. This material was dissolved in iPrOH and acidified to a pH of 3 with concentrated HCl. The acidified solution was diluted with ether resulting in precipitation of the monohydrochloride salt which was collected by filtration and dried under vacuum to provide 11.21 g of 4-[2-(1-methylethoxy)phenyl]piperidine hydrochloride as a beige powder. The structure was supported by MS. The free base was obtained by extraction into $CHCl_3$ from 1N NaOH, drying ($MgSO_4$), and filtration.

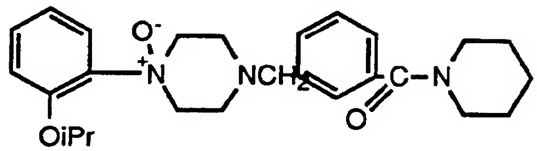
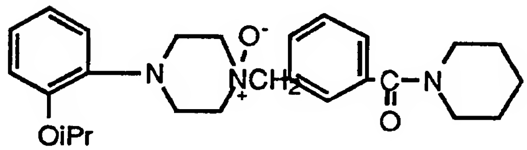
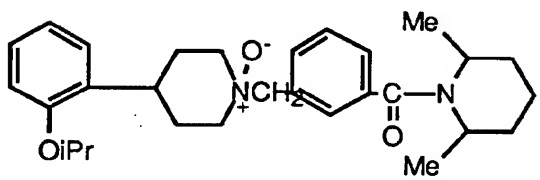
In 100 ml of 2-pyridone, 4-(2-isopropoxyphenyl)piperidine (5.69 g, 0.0259 mol), 3-(chloromethyl)benzoyl-2,6-cis-dimethylpiperidine (6.91 g, 0.0259 mol), and sodium carbonate (8.75 g, .0825 mol) were combined and heated to 70°C. After 2.5 hours, the oil bath was removed and the reaction cooled to room temperature while stirring overnight. The crude reaction mixture was diluted with chloroform and then subjected to flash chromatography on silica with chloroform as eluant resulting in the isolation of slightly impure product (7.95 g; 68%). Conversion to its corresponding HCl salt, followed by neutralization provided pure free-base product. The assigned structure was supported by NMR and MS. Elemental Analysis

calculated for $C_{29}H_{40}N_2O_2 \cdot 0.25H_2O \cdot HCl$: C, 71.14; H, 8.54; N, 5.72; Cl, 7.24; H_2O, 0.92. Found: C, 71.20; H, 8.83; N, 5.59; Cl, 6.99; H_2O, 0.55.

A solution of m-chloroperoxybenzoic acid (0.80 g, 4.63 mmol) in $CHCl_3$ (10 mL) was added dropwise to a suspended mixture of 1-[3-[[4-[2-(1-methylethoxy)phenyl]-1-piperidinyl-1-oxide]methyl]benzoyl]-cis-2,6-dimethylpiperidine in $CHCl_3$ (10 mL) while stirring at 0°C. The reaction was continued overnight. The solvent was then removed and the residue was purified on a silica gel column ($CHCl_3$/MeOH, 100:0 to 90:10). The solid which was obtained was recrystallized from $CHCl_3$/hexane to give the title compound as a white powder (0.70 g), m.p. 104-106°C. ^1H NMR (CD_3OD, 400 MHz) δ 7.7 (s, 1H), 7.58 (d, 1H), 7.53 (t, 1H), 7.45 and 7.35 (both d, 1H each), 7.14 (t, 1H), 6.95 (d, 1H), 6.9 (t, 1H), 4.6 (m, 1H), 4.45 (s, 2H), 3.5 (t, 2H), 3.2 (m, 2H), 2.4 (q, 2H), 1.93 (m, 1H), 1.7 (m, 10 H), and 1.3 (d, 6H). The mass spectra also supported the assigned structure.

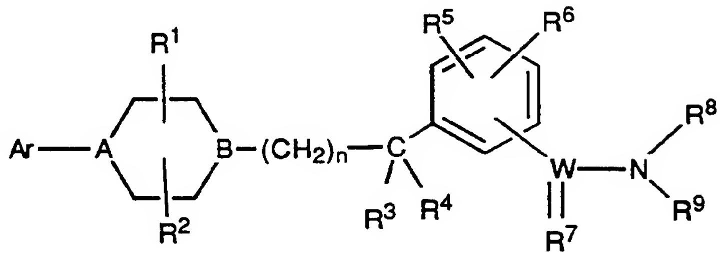
Elemental Analysis calculated for $C_{29}H_{40}N_2O_3 \cdot H_2O \cdot CHCl_3$: C, 69.50; H, 8.20; N, 5.54; H_2O, 2.18. Found: C, 69.23; H, 8.36; N, 5.43; H_2O, 2.09.

TABLE 1

Structure	Compd. #	% CAR at 15 mg/kg (Loss of escape)	Dopamine-2 (nM)
	1	-91.7 (44.8)	140
	2	-87.6 (31.5)	355
	3	-37.7 (0.4)	371

WE CLAIM:

1. A compound represented by the formula **I**:



I

wherein

A is N, CH, or N^+-O^-;

B is N, or N^+-O^-; with the proviso that when A is N or CH, B must be N^+-O^-; and when A is N^+-O^-, B must be N.

W is C or SO;

R^1 and R^2 are H or C_1-C_4 alkyl .

n = 0-4;

R^3 and R^4 are either both H, or one of them is H and the other is C_1-C_4 alkyl or hydroxyl, or both are taken together as oxygen to constitute a carbonyl group, with the proviso that when n=0, R^3 and R^4 can not be taken together as oxygen.

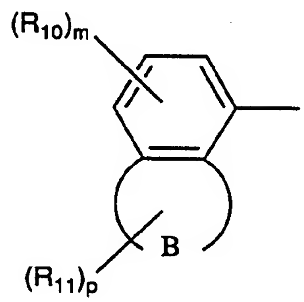
R^5 and R^6 are independently selected from any one of H, C_1-C_8 alkyl, C_1-C_8 alkoxy, nitro, halogen, haloalkyl, C_1-C_8 alkylthio, amino, C_1-C_8 mono- or dialkyl amino, or C_1-C_8 alkylamido;

R^7 is O or S where W is C; R^7 is O where W is SO;

R^8 and R^9 are independently selected from any one of H, C_1-C_8 alkyl, C_1-C_8 aminoalkyl, phenyl, substituted phenyl, aralkyl wherein the alkyl portion is C_1-C_8, C_1-C_8 acyl, C_3 to C_{10} cycloalkyl; or -NR^8R^9 may be taken together to form a ring having 4-10 ring atoms, which ring may be saturated or unsaturated, substituted or unsubstituted, and may contain

one or more hetero atoms in addition to the ring N, such as S, O or N within the ring; or optionally $-NR^8R^9$ may be combined with a 2-4 membered carbon moiety to form a fused bicyclic ring, which may be saturated or unsaturated, and unsubstituted or substituted; or optionally NR^8R^9 may be combined with a 4 membered moiety containing at least two carbon atoms and up to two hetero atoms selected from S or O, to form a spirocycle ring system; which may be saturated, or unsaturated, substituted or unsubstituted, or the acceptable acid addition salt, hydrate, solvate, isomers or racemates thereof.

2. The compound of claim 1, wherein when Ar is a fused ring system represented by the formula **II**:



II

wherein B together with the 2 carbon atoms of the phenyl group forms an entirely or partly unsaturated cyclic group having 5-7 ring atoms and within the ring 0-3 hetero atoms from any of O, S or N, with the proviso that the sum of the number of O and S atoms is at most 2, and that the N atoms in the ring may be substituted with R^{12} selected from any one of H, alkyl, hydroxyalkyl or acyl;

wherein R^{10} and R^{11} are independently selected from any one of alkyl, C_3-C_7 cycloalkyl, phenyl, substituted phenyl, heteroaryl, hydroxyalkyl, alkoxyalkyl, alkoxy, aryloxy, alkylthio, arylthio, mono- or diarylamino, hydroxyl, amino, alkyl-, alkoxy-, amino-, mono- or dialkylamino-carbonyl, nitro, cyano, halogen, trifluoromethyl, trifluoromethoxy, amino-, or mono-, or dialkylamino-sulfonyl; R^{10} may also be oxo or thioxo; m is 0-3 and p is 0-2.

3. The compound of claim 2, wherein B forms together with the two carbon atoms of the phenyl group an entirely or partly unsaturated ring consisting of 5 ring atoms, at least one of which is an oxygen atom;

wherein R^{10} and R^{11} are independently selected from any one of alkyl, alkoxy, hydroxyl, nitro, cyano, halogen, trifluoromethyl, with the proviso that R_6 is in the meta or ortho position in relation to the piperazine ring; wherein each of m and p has the value of 0-2.

4. The compound of claim 3, wherein m and p each equal 0.

5. The compound of claim 2, wherein when R^{10} or R^{11} comprise an alkyl group and such group contains 1-5 carbon atoms and when R^{10} or R^{11} comprise a cycloalkyl group the ring system that has 3-7 ring atoms and not more than 10 carbon atoms including substituents.

6. The compound of claim 1, wherein Ar is phenyl substituted with an alkoxy group; A is N; n is 0; and R^1, R^2, R^3, and R^4 is H.

7. The compound of claim 6, wherein the alkoxy group is i-propoxy.

8. The compound of claim 1, wherein R^8R^9 are taken together as $-NR^8R^9$ to form a ring having 4-8 ring atoms, whcih ring is saturated and contains up to one more hetero atom selected from any of N, O or S, in addition to the N.

9. The compound of claim 8, whrein the 4-8 membered ring is unsubstituted.

10. The compound of claim 8, wherein the 4-8 membered ring is substituted with one or more of C_1-C_8 alkyl, C_1-C_8 alkoxy, phenyl, substituted phenyl, hydroxy, aralkyl, oxo or thio, wherein phenyl may be substituted with one or more of C_1-C_8 alkyl, C_1-C_8 alkoxy, halogen, trifluoromethyl, C_1-C_8 alkyl, dialkylamino wherein each alkyl is C_1-C_8, C_1-C_8 alkylamino, nitro or mono- or dialkylamino sulfonyl wherein each alkyl is C_1-C_8.

11. The compound of claim 1, wherein the $-NR^8R^9$ 4-10 membered ring is saturated prior to being combined with the 2-4 membered carbon moiety to form a fused ring.

12. The compound of claim 1, wherein the 4 membered moiety used to form the spirocycle ring system contains 2 oxygen atoms separated by 2 carbon atoms.

13. The compound of claim 6, wherein W is C, wherein R^5 is O and wherein each of R^6 and R^7 are H.

14. The compound of claim 6, wherein W is SO, wherein R^5 is O and wherein each of R^6 and R^7 are H.

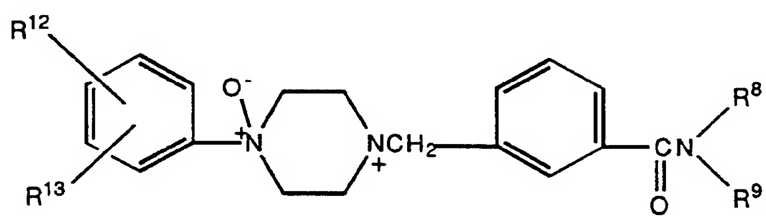
15. The compound of claim 6, wherein W is C, wherein R^5 is S and wherein each of R^6 and R^7 is H.

16. The compound of claim 13, wherein $-NR^8R^9$ are taken together to form a saturated ring having 6 ring atoms.

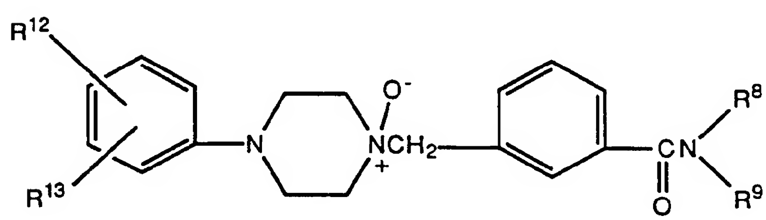
17. The compound of claim 1, wherein Ar is substituted phenyl, and it is substituted with one or more of C_1-C_8 alkyl, C_1-C_8 alkoxy, cyano, C_1-C_8 alkylthio, halogen, haloalkyl, trifluoromethyl, amino, or mono- or di-alkylamino.

18. The compound of claim 12, wherein Ar is substituted with one or more of C_1-C_8 alkyl, C_1-C_8 alkoxy, halogen or haloalkyl and wherein $-NR^8R^9$ are taken together to form a saturated ring having 4-8 carbon ring atoms with the N being the only hetero atom in the ring

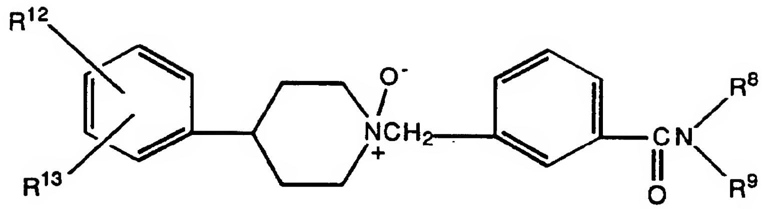
19. A compound selected from any of:



Ia



Ib



Ic

wherein R^8 and R^9 are independently selected from any one of H, C_1-C_8 alkyl, phenyl, substituted phenyl, C_6-C_{15} aralkyl, C_1-C_8 acyl, C_4-C_{10} cycloalkyl; or -NR^8R^9 may be taken together to form a ring, substituted or unsubstituted having 4-10 ring atoms, which ring may be saturated or unsaturated, and may contain one or more hetero atoms selected from S, O, N within the ring; or -NR^8R^9 may be taken together to form a spiro ring system, substituted or unsubstituted, which ring system may be saturated or unsaturated;

wherein R^{12} and R^{13} are selected from any one of H, C_1-C_8 alkyl, C_1-C_8 alkoxy, cyano, C_1-C_8 alkylthio, halogen, haloalkyl, amino, or C_1-C_8 mono- or dialkylamino, or the pharmaceutically acceptable acid addition salts, hydrates, solvates, isomers or racemates thereof.

20. The compound of claim 19 wherein R^{12} is C_1-C_8 alkoxy.

21. The compound of claim 20, wherein -NR^8R^9 are taken together to form a fully saturated ring containing 5 ring carbon atoms.

22. The compound of claim 21, wherein the NR^8R9 ring is independently substituted with any C_1-C_8 alkyl.

23. The compound of claim 21, wherein the NR^8R^9 ring is unsubstituted.

24. The compound of claim 19 represented by the formula 1-[3-[[4-[2-(1-methylethoxy)phenyl]-4-oxide-1-piperazinyl]methyl]benzoyl]piperidine.

25. The compound of claim 19 represented by the formula 1-[3-[[4-[2-(1-methylethoxy)phenyl]-1-piperazinyl-1-oxide]methyl]benzoyl]piperidine.

26. The compound of claim 1 represented by the formula 1-[3-[[4-[2-(1-methylethoxy)phenyl]-1-piperidinyl-1-oxide]methyl]benzoyl]-cis-2,6-dimethylpiperidine.

27. A composition comprising the compound of claim 1, and a pharmaceutically acceptable carrier, said compound being present in a therapeutically effective amount.

28. A method for treating psychotic conditions in animals comprising administering to an animal in need of such treatment the compound of claim 1 in an amount sufficient to treat such condition.

29. The method of claim 26, wherein the condition is schizophrenia.

30. The method of claim 26, wherein Ar is phenyl substituted with a C_1-C_8 alkoxy.

31. The compound of claim 27, wherein the NR^8R^9 ring is independently substituted with any of C_1-C_8 alkyl.

32. The compound of claim 27, wherein the NR^8R^9 ring is unsubstituted.

33. The method of claim 28, wherein -NR^8R^9 are taken together with the N to form a fully saturated ring containing 5 carbon atoms.

34. The method of claim 27, represented by the formula 1-[3-[[4-[2-(1-methylethoxy)phenyl]-4-oxide-1-piperazinyl]methyl]benzoyl]piperidine.

35. The method of claim 27, represented by the formula 1-[3-[[4-[2-(1-methylethoxy)phenyl]-1-piperazinyl-1-oxide]methyl]benzoyl]piperidine.

36. The method of claim 27, represented by the formula 1-[3-[[4-[2-(1-methylethoxy)phenyl]-1-piperidinyl-1-oxide]methyl]benzoyl]-cis-2,6-dimethylpiperidine.

INTERNATIONAL SEARCH REPORT

Intc onal Application No
PCT/US 94/14850

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D211/94 C07D295/22 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A,93 04682 (MCNEILAB) 18 March 1993 cited in the application see the whole document ---	1-36
Y	XENOBIOTICA, vol.23, no.5, 1993 pages 495 - 508 GORROD, FANG 'On the metabolism of haloperidol' see page 102, line 4 - line 7 ---	1-36
P,A	FR,A,2 697 251 (SYNTHELABO) 29 April 1994 see the whole document -----	1-36

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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Date of the actual completion of the international search	Date of mailing of the international search report
13 April 1995	27.04.95

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ional Application No
PCT/US 94/14850

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		AU-A- 2659992	05-04-93
		CA-A- 2095826	12-03-93
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		EP-A- 0563345	06-10-93
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FR-A-2697251	29-04-94	NONE	